Molecular Mechanisms Underlying Human Cardiac Cell Junction Maturation and Disease Using Human iPSC

Grant Award Details

Molecular Mechanisms Underlying Human Cardiac Cell Junction Maturation and Disease Using Human iPSC

Grant Type: Basic Biology III

Grant Number: RB3-05103

Project Objective: The project objective is to develop a human iPSC-derived model of arrhythmogenic right ventricular cardiomyopathy (ARVC) and use this model to study mechanisms of the disease including the role of CSN6, a novel cardiac desmosomal cell junction interacting protein.

Investigator:

Name:	Farah Sheikh
Institution:	University of California, San Diego
Type:	PI

Disease Focus: Heart Disease, Pediatrics

Human Stem Cell Use: iPS Cell

Cell Line Generation: iPS Cell

Award Value: $1,341,955

Status: Closed

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Reporting Period: Year 3

View Report

Grant Application Details

Application Title: Molecular Mechanisms Underlying Human Cardiac Cell Junction Maturation and Disease Using Human iPSC

Public Abstract: Heart disease is the number one cause of death and disability in California and in the United States. Especially devastating is Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC), an inherited form of heart disease associated with a high frequency of arrhythmias and sudden cardiac death in young people, including young athletes, who despite their appearance of health are struck down by this type of heart disease. Even though it is inherited, early detection is hindered because people carrying the genetic code have highly variable clinical symptoms, making ARVC and catastrophic cardiac events very hard to predict and avoid. Evidence suggests that this heart disease is caused by mistakes in the genetic code essential for holding the mechanical integrity of heart muscle cells together or cell junctions. What is missing is an understanding of the basic biology of these heart muscle cell junctions in humans and appropriate human model systems to study their dynamics in heart disease, which is important since other heart diseases also share some of these same heart cell defects. Our goal is to understand the basic biology of how human heart muscle cell junctions mature and what happens in disease, by studying ARVC. Human iPS cells are a unique population of stem cells from our own tissues, such as skin, that have the same genetic information as the rest of our bodies. Thus, hiPS from people who carry the ARVC heart disease mistakes can be used in our laboratory to provide a true human model of that disease. We will generate heart muscle cells from hiPS from normal and ARVC donors that carry mistakes in the genetic code for cell junction components. We have identified new pathways that may be important causes of ARVC, thus we will also use our hiPS lines, to confirm whether these new pathways are truly important in human ARVC disease progression and if our approaches reverse disease progression. Characterization of our hiPS derived heart cells can also be exploited for translational medicine to predict an individual's heart cell response to drug treatment and provides a promising platform to identify new drugs for heart diseases, such as ARVC, which are currently lacking in the field. Recent advances in stem cell biology have highlighted the unique potential of hiPS to be used in the future as a source of cells for cell-based therapies for heart disease. However, prior to clinical application, a detailed understanding of the basic biology and maturation of these hiPS into heart muscle cells is required. Our studies seek to advance our understanding of how cell-cell junctions mature in hiPS and highlight tools that influence the microenvironment of the hiPS in a dish, to accelerate this process. This knowledge can also be exploited in regenerative medicine to achieve proper electromechanical integration of cardiac stem cells when using stem cells for heart repair, to improve longterm successful clinical outcomes of cardiac stem cell therapies.

Statement of Benefit to California:	Heart disease is the number one cause of death and disability within the United States and the rates are calculated to be even higher for citizens of the State of California when compared to the rest of the nation. These diseases place tremendous financial burdens on the people and communities of California, which highlights an urgency to understand the underlying molecular basis of heart diseases as well as find more effective therapies to alleviate these growing burdens. Our goal is to improve heart health and quality of life of Californians by generating human stem cell models from people with an especially devastating form of genetic heart disease that affects young people and results in sudden cardiac death, to improve our molecular and medical understanding of how cardiac cells go wrong in the early stages of heart disease in humans. We will also test current drugs used to treat heart disease and new candidate pathways, that we have uncovered, to determine if and how they reverse and intervene with these defects. We believe that our model systems have tremendous potential in being used to diagnose, test an individual's heart cell's response to drug treatment, as well as predict severity of symptoms in heart diseases at an early stage, to monitor drug treatment strategies for the heart. We believe our studies also have a direct impact on regenerative medicine as a therapy for Californians suffering from heart disease, since data from our studies can identify ways to improve cardiac stem cell integration into the diseased heart when used for repair, as a way to improve long-term successful clinical outcomes of cardiac stem cell therapies. We also believe that our development of multiple human heart disease stem cells lines with unique genetic characteristics could be of tremendous value to biotechnology companies and academic researchers interested in large scale drug screening strategies to identify more effective compounds to rescue defects and treat Californians with heart disease, as well as provide important economic revenue and resources to California, which is stimulated by the development of businesses interested in developing these therapies further.